ANDA 74-701

JUL 7 1996

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated June 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

Reference is also made to your amendments dated February 7 and 16, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Triamterene and Hydrochlorothiazide Capsules USP, 37.5/25 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Dyazide® Capsules, 37.5/25 mg of SmithKline Beecham Pharmaceuticals]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Office of Generic Drugs
Center for Drug Evaluation and Research

TMHZ:R1

APPROVED JUN 7 1996

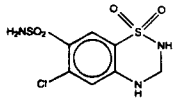
TRIAMTERENE and HYDROCHLOROTHIAZIDE CAPSULES, USP

37.5 mg/25 mg

DESCRIPTION: Each triamterene and hydrochlorothiazide capsule for oral administration contains hydrochlorothiazide 25 mg and triamterene 37.5 mg. Hydrochlorothiazide is a diuretic/antihypertensive agent and triamterene is an antikaliuretic agent.

Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute aqueous sodium hydroxide and dimethylformamide. It is sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and its structural formula is:

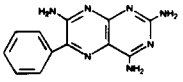


MW: 297.75

Molecular Formula: $C_7H_8ClN_3O_4S_2$

At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic acid, sparingly soluble in methoxyethanol and very slightly soluble in alcohol.

Triamterene is 2,4,7-triamino-6-phenylpteridine and its structural formula is:



MW: 253.27

Molecular Formula: $C_{12}H_{11}N_7$

Inactive ingredients consist of colloidal silicon dioxide, croscarmellose sodium, gelatin, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, polyethylene glycol, polysorbate 80, propylene glycol, silicon dioxide, sodium bicarbonate, sodium lauryl sulfate, synthetic black iron oxide, titanium dioxide, yellow iron oxide, D&C Yellow #10 Aluminum Lake, FD&C Blue #1, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, and FD&C Red #40 Aluminum Lake.

Triamterene and Hydrochlorothiazide Capsules, USP 37.5 mg/25 mg meet USP *Dissolution Test 1*.

CLINICAL PHARMACOLOGY: The triamterene and hydrochlorothiazide capsule is a diuretic/antihypertensive drug product that combines natriuretic and antikaliuretic effects. Each component complements the action of the other. The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

The triamterene component of triam-

MW. 253.2

Molecular Formula: $C_{12}H_{11}N_7$

Inactive ingredients consist of colloidal silicon dioxide, croscarmellose sodium, gelatin, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, polyethylene glycol, polysorbate 80, propylene glycol, silicon dioxide, sodium bicarbonate, sodium lauryl sulfate, synthetic black iron oxide, titanium dioxide, yellow iron oxide, D&C Yellow #10 Aluminum Lake, FD&C Blue #1, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, and FD&C Red #40 Aluminum Lake.

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The triamterene component of triamterene and hydrochlorothiazide capsules exerts its diuretic effect on the distal renal tubule to inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic activity is limited by the amount of sodium reaching its site of action. Although it blocks the increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone) it is not a competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized rats and patients with Addison's disease. As a result, the dose of triamterene required is not proportionally related to the level of mineralocorticoid activity, but is dictated by the response of the individual patients, and the kaliuretic effect of concomitantly administered drugs. By inhibiting the distal tubular exchange mechanism, triamterene maintains or increases the sodium excretion and reduces the excess loss of potassium, hydrogen and chloride ions induced by hydrochlorothiazide. As with hydrochlorothiazide, triamterene may reduce glomerular filtration and renal plasma flow. Via this mechanism it may reduce uric acid excretion although it has no tubular effect on uric acid reabsorption or secretion. Triamterene does not affect calcium excretion. No predictable antihypertensive effect has been demonstrated for triamterene.

Duration of diuretic activity and effective dosage range of the hydrochlorothiazide and triamterene components of triamterene and hydrochlorothiazide capsules are similar. Onset of diuresis with triamterene and hydrochlorothiazide takes place within 1 hour, peaks at 2 to 3 hours and tapers off during the subsequent 7 to 9 hours.

Triamterene and hydrochlorothiazide capsules are well absorbed.

It has been reported that upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameters were determined:

	AUC(0–48) ng•hr/mL (±SD)	Cmax ng/mL (±SD)	Median Tmax hrs	Ae mg (±SD)
triamterene	148.7 (87.9)	46.4 (29.4)	1.1	2.7 (1.4)
hydroxytriamterene sulfate	1865 (471)	720 (364)	1.3	19.7 (6.1)
hydrochlorothiazide	834 (177)	135.1 (35.7)	2.0	14.3 (3.8)

where AUC(0-48), Cmax, Tmax and Ae represent area under the plasma concentration versus time plot, maximum plasma concentration, time to reach Cmax and amount excreted in urine over 48 hours.

One triamterene and hydrochlorothiazide capsule is bioequivalent to a single-entity 25 mg hydrochlorothiazide tablet and 37.5 mg triamterene capsule used in the double-blind clinical trial below. (See Clinical Trials.)

In a limited study involving 12 subjects, coadministration of triamterene and hydrochlorothiazide capsules with a high-fat meal resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90% confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.26); (2)

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Clinical Trials: A placebo-controlled, double-blind trial was conducted to evaluate the efficacy of triamterene and hydrochlorothiazide capsules. This trial demonstrated that triamterene and hydrochlorothiazide capsules (37.5 mg triamterene/25 mg hydrochlorothiazide) were effective in controlling blood pressure while reducing the incidence of hydrochlorothiazide-induced hypokalemia. This trial involved 636 patients with mild to moderate hypertension controlled by hydrochlorothiazide 25 mg daily and who had hypokalemia (serum potassium <3.5 mEq/L) secondary to the hydrochlorothiazide. Patients were randomly assigned to 4 weeks' treatment with once-daily regimens of 25 mg hydrochlorothiazide plus placebo, or 25 mg hydrochlorothiazide combined with one of the following doses of triamterene: 25 mg, 37.5 mg, 50 mg or 75 mg.

Blood pressure and serum potassium were monitored at baseline and throughout the trial. All five treatment groups had similar mean blood pressure and serum potassium concentrations at baseline (mean systolic blood pressure range: 137 ± 14 mmHg to 140 ± 16 mmHg; mean diastolic blood pressure range: 86 ± 9 mmHg to 88 ± 8 mmHg, mean serum potassium range: 2.3 to 3.4 mEq/L with the majority of patients having values between 3.1 and 3.4 mEq/L).

While all triamterene regimens reversed hypokalemia, at week 4 the 37.5 mg regimen proved optimal compared with the other tested regimens. On this regimen, 81% of the patients had a significant ($p<0.05$) reversal of hypokalemia vs. 59% of patients on the placebo/hydrochlorothiazide regimen. The mean serum potassium concentration on 37.5 mg triamterene went from 3.2 ± 0.2 mEq/L at baseline to 3.7 ± 0.3 mEq/L at week 4, a significantly greater ($p<0.05$) improvement than that achieved with placebo/hydrochlorothiazide (i.e., 3.2 ± 0.2 mEq/L at baseline and 3.5 ± 0.4 mEq/L at week 4). Also, 51% of patients in the 37.5 mg triamterene group had an increase in serum potassium of ≥0.5 mEq/L at week 4 vs. 33% in the placebo group. The 37.5 mg triamterene/25 mg hydrochlorothiazide regimen also maintained control of blood pressure; mean supine systolic blood pressure at week 4 was 138 ± 21 mmHg while mean supine diastolic blood pressure was 87 ± 13 mmHg.

INDICATIONS AND USAGE: This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules are indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone.

Triamterene and hydrochlorothiazide capsules are also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Triamterene and hydrochlorothiazide capsules may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since triamterene and hydrochlorothiazide capsules may enhance the action of these agents, dosage adjustments may be necessary.

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Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances this edema may cause extreme discomfort which is not relieved by rest. In these cases a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS: Antikaliuretic Therapy and Potassium Supplementation: Triamterene and hydrochlorothiazide capsules should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride or other formulations containing triamterene. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with triamterene and hydrochlorothiazide capsules except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function: Triamterene and hydrochlorothiazide capsules are contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

Hypersensitivity: Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

Hyperkalemia: Triamterene and hydrochlorothiazide capsules should not be used in patients with preexisting elevated serum potassium.

WARNINGS: Hyperkalemia:

> Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-sparing diuretic combinations, including triamterene and hydrochlorothiazide capsules. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving triamterene and hydrochlorothiazide capsules, when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes. If hyperkalemia is present, triamterene and hydrochlorothiazide capsules should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/liter more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride injection, sodium bicarbonate injection and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence

either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

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The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS section). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be reduced and the plasma levels increased following triamterene and hydrochlorothiazide administration to elderly patients and patients with impaired renal function.

Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be frequently monitored if triamterene and hydrochlorothiazide capsules are used in diabetic patients.

Metabolic or Respiratory Acidosis: Potassium-sparing therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be associated with rapid elevations in serum potassium levels. If triamterene and hydrochlorothiazide capsules are employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS: Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer triamterene and hydrochlorothiazide capsules cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases discontinue triamterene and hydrochlorothiazide capsules for a few days. Attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion.

Hypokalemia: Hypokalemia is uncommon with triamterene and hydrochlorothiazide capsules; but, should it develop, corrective measures should be taken such as potassium supplementation or increased intake of potassium-rich foods. Institute such measures cautiously with frequent determinations of serum potassium levels, especially in patients receiving digitalis or with a history of cardiac arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by repeat serum potassium determinations, triamterene and hydrochlorothiazide capsules should be discontinued and potassium

chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to other coexisting conditions and treated accordingly.

Electrolyte Imbalance: Electrolyte imbalance, often encountered in such conditions as heart failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be considered during triamterene and hydrochlorothiazide therapy when using high doses for prolonged periods or in patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and are particularly important if the patient is vomiting excessively or receiving fluids parenterally. Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal symptoms.

Hypochloremia: Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Renal Stones: Triamterene has been found in renal stones in association with the other usual calculus components. Triamterene and hydrochlorothiazide capsules should be used with caution in patients with a history of renal stones.

Laboratory Tests: ***Serum Potassium:*** The normal adult range of serum potassium is 3.5 to 5.0 mEq per liter with 4.5 mEq often being used for a reference point. If hypokalemia should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods.

Institute such measures cautiously with frequent determinations of serum potassium levels. Potassium levels persistently above 6 mEq per liter require careful observation and treatment. Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in plasma pH may cause a decrease in plasma potassium concentration and an increase in the intracellular potassium concentration. Discontinue corrective measures for hypokalemia immediately if laboratory determinations reveal an abnormal elevation of serum potassium. Discontinue triamterene and hydrochlorothiazide capsules and substitute a thiazide diuretic alone until potassium levels return to normal.

Serum Creatinine and BUN: Triamterene and hydrochlorothiazide may produce an elevated blood urea nitrogen level, creatinine level or both. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather than renal toxicity; levels usually return to normal when triamterene and hydrochlorothiazide capsules are discontinued. If azotemia increases, discontinue triamterene and hydrochlorothiazide capsules. Periodic BUN or serum creatinine determinations should be made, especially in elderly patients and in patients with suspected or confirmed renal insufficiency.

Serum PBI: Thiazide may decrease serum PBI levels without sign of thyroid disturbance.

Parathyroid Function: Thiazides should be discontinued before carrying out tests for parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as bone resorption and peptic ulceration have not been seen.

Drug Interactions: ***Angiotensin-converting enzyme inhibitors:*** Potassium-sparing agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to an increased risk of hyperkalemia.

Oral hypoglycemic drugs: Concurrent use with chlorpropamide may increase the risk of severe hyponatremia.

Nonsteroidal anti-inflammatory drugs: A possible interaction resulting in acute renal failure has been reported in a few patients on triamterene and hydrochlorothiazide capsules when treated with indomethacin, a nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with triamterene and hydrochlorothiazide capsules.

Lithium: Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with triamterene and hydrochlorothiazide capsules.

Surgical considerations: Thiazides have been shown to decrease arterial responsiveness to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine (an effect

anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with triamterene and hydrochlorothiazide capsules.

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Other Considerations: Concurrent use of hydrochlorothiazide with amphotericin B or corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

Thiazides may add to or potentiate the action of other antihypertensive drugs. See INDICATIONS AND USAGE for concomitant use with other antihypertensive drugs.

The effect of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary.

Triamterene and hydrochlorothiazide may raise the level of blood uric acid; dosage adjustments of antigout medication may be necessary to control hyperuricemia and gout.

The following agents given together with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of triamterene, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq per liter of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes (most contain substantial amounts of potassium).

Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake.

Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene.

The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine.

Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus, triamterene and hydrochlorothiazide will interfere with the fluorescent measurement of quinidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** Long-term studies have not been conducted with the triamterene/hydrochlorothiazide combination, or with triamterene alone.

Hydrochlorothiazide: Two-year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose (MRHD) for the hydrochlorothiazide component of triamterene and hydrochlorothiazide capsules at 50 mg/day (or 1 mg/kg/day based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Mutagenesis: Studies of the mutagenic potential of the triamterene/ hydrochlorothiazide combination, or of triamterene alone have not been performed.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility: Studies of the effects of the triamterene/hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted

vitro CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43 to 1300 mcg/mL. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility: Studies of the effects of the triamterene/hydrochlorothiazide combination, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

Pregnancy: *Category C: Teratogenic Effects: Triamterene and hydrochlorothiazide:* Animal reproduction studies to determine the potential for fetal harm by triamterene and hydrochlorothiazide have not been conducted. However, a One Generation Study in the rat approximated triamterene and hydrochlorothiazide capsules' composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of triamterene and hydrochlorothiazide capsules in pregnancy has not been established since there are no adequate and well-controlled studies with triamterene and hydrochlorothiazide in pregnant women. Triamterene and hydrochlorothiazide capsules should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene: Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 3000 for mice and 1000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on body-surface area, there was no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Teratogenic Effects: Thiazides and triamterene have been shown to cross the placental barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possible other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides and triamterene in combination have not been studied in nursing mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted in human breast milk. If use of the combination drug product is deemed essential, the patient should stop nursing.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse effects are listed in decreasing order of frequency; however, the most serious adverse effects are listed first regardless of frequency. The serious adverse effects associated with triamterene and hydrochlorothiazide capsules have commonly occurred in less than 0.1% of patients treated with this product.

Hypersensitivity: anaphylaxis, rash, urticaria, photosensitivity.

Cardiovascular: arrhythmia, postural hypotension.

Metabolic: diabetes mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia.

Gastrointestinal: jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.

Renal: acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.

Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.

Musculoskeletal: muscle cramps.

Central Nervous System: weakness, fatigue, dizziness, headache, dry mouth.

Miscellaneous: impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:

Central Nervous System: paresthesias.

composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.
Hematologic: leukopenia, thrombocytopenia and purpura, megaloblastic anemia.
Musculoskeletal: muscle cramps.
Central Nervous System: weakness, fatigue, dizziness, headache, dry mouth.
Miscellaneous: impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:
Central Nervous System: paresthesias, vertigo.
Opthalmic: xanthopsia, transient blurred vision.
Respiratory: allergic pneumonitis, pulmonary edema, respiratory distress.
Other: necrotizing vasculitis, exacerbation of lupus.
Hematologic: aplastic anemia, agranulocytosis, hemolytic anemia.
Neonate and Infancy: thrombocytopenia and pancreatitis - rarely, in newborns whose mothers have received thiazides during pregnancy.

OVERDOSAGE: Electrolyte imbalance is the major concern (see WARNINGS section). Symptoms reported include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face and hyperactive deep tendon reflexes. If hypotension occurs, it may be treated with pressor agents such as norepinephrine to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid balance. Induce immediate evacuation of the stomach through emesis or gastric lavage. There is no specific antidote.

Reversible acute renal failure following ingestion of 50 tablets of a product containing a combination of 50 mg triamterene and 25 mg hydrochlorothiazide has been reported.

Although triamterene is largely protein-bound (approximately 67%), there may be some benefit to dialysis in cases of overdosage.

DOSAGE AND ADMINISTRATION: The usual dose of triamterene and hydrochlorothiazide capsules is one or two capsules given once daily, with appropriate monitoring of serum potassium and of the clinical effect. (See WARNINGS, Hyperkalemia.)

HOW SUPPLIED: Triamterene and Hydrochlorothiazide Capsules, USP are available containing 37.5 mg triamterene and 25 mg hydrochlorothiazide in opaque olive and opaque rich yellow capsules marked in black ink with MYLAN over 2537 on both body and cap. They are available as follows:

NDC 0378-2537-01
bottles of 100 capsules
NDC 0378-2537-10
bottles of 1000 capsules

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
PROTECT FROM LIGHT.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc
Morgantown, WV 26505

REVISED FEBRUARY 1996
TMHZ:R1

1. CHEMISTRY REVIEW NO 2

2. ANDA 74-701

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION listed in Orange Book

5. SUPPLEMENT(s) NA 6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Triamterene and Hydrochlorothiazide, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: NA

9. AMENDMENTS AND OTHER DATES:
June 16, 1995: Date of submission
February 16, 1996: Amendment (subject of review)
February 7, 1996: Bio correspondence

10. PHARMACOLOGICAL CATEGORY 11. Rx
diuretic and renal tuble inhibitor

12. RELATED IND/NDA/DMF(s) see #37

13. DOSAGE FORM 14. POTENCY
37.5 mg/ 25 mg in a #4 olive opaque cap /rich yellow opaque body imprinted with "Mylan 2537 in black ink

16. RECORDS AND REPORTS NA

17. COMMENTS
The deficiencies, response and review comments are in italics.

18. CONCLUSIONS AND RECOMMENDATIONS : Approvable when labeling and bio are found to be satisfactory

19. REVIEWER: Dave Gill
DATE COMPLETED: March 8, 1996

cc: ANDA 74-701
DUP Jacket
Division File

Endorsements:
HFD-623/D. Gill/[redacted]/S/[redacted]/3-7-96
HFD-623/A. Rudman, Ph.D./[redacted]/S/[redacted] 3/13/96 pending sat. review
no [redacted]/S/[redacted].
x:\new\firmsam\Mylan\ltrs&rev\74701ap.d

F/T by

RECORD OF TELEPHONE CONVERSATION

I called Mylan and spoke to John O'Donnell concerning ANDA 74-701. The Agency sent out an approval letter to this ANDA on June 7, 1996. It was noted that a MINOR Amendment was submitted on April 29, 1996 was not addressed in the approval letter. This was an oversight on the Agency's part. The submission included revised insert labeling which reflected that the product meets USP Dissolution Test 3. I told John that they could go ahead and use this insert labeling though technically the previous insert was the one that had been approved. This change is annual reportable and thus the new insert can be implemented immediately. Mr. O'Donnell expressed a concern that BIO is not aware of this change in the Dissolution test # since it was recently placed into effect by the USP (5-15-96) and asked if I could help him with this or if he should call Jason Gross. I directed him to call Jason regarding this.

Division of Labeling + Program Support

DATE
June 12, 1996

ANDA NUMBER
74-701

IND NUMBER

TELECON

INITIATED BY	**MADE**
APPLICANT/ SPONSOR	**X BY TELE.**
X FDA	**_ IN PERSON**

PRODUCT NAME
Triamterene and HCTZ capsules USP 37.5 mg/25 mg

FIRM NAME
Mylan Pharmaceuticals Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
John O'Donnell
Regulatory Affairs

TELEPHONE NUMBER
(304) 599-2595

SIGNATURE
[redacted] /S/ [redacted] 6/12/96

ANDA 74-701

MAY 31 1996

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Triamterene and Hydrochlorothiazide Capsules USP, 37.5 mg/25 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of 0.1 M acetic acid containing 1% of polysorbate 20, at 37°C using USP 23 apparatus 2 (paddle) at 100 rpm. The test product should meet the following specifications:

   Not less than (b)(4) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes for Triamterene.

   Not less than (b)(4) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes for Hydrochlorothiazide.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 2 4 1996

Triamterene/Hydrochlorothiazide
37.5 mg/25 mg Capsule
ANDA # 74-701
Reviewer: Moheb H. Makary
WP 74701SD.296

Mylan Pharmaceutical.
Morgantown, WV.
Submission Date:
February 7, 1996

Review Of Bioequivalence Study And Dissolution Data

I. Objective:

The objective of this study is to compare the plasma levels of triamterene, triamterene sulfate and hydrochlorothiazide as well as their urinary excretion, after administration of single dose of 75 mg/50 mg (2 x37.5 mg/25 mg Capsules) of the test formulation (Mylan's triamterene/hydrochlorothiazide, 37.5 mg/25 mg capsule) with that of SmithKline Beecham reference product (Dyazide^{R} capsule 37.5 mg/25 mg) under nonfasting conditions.

The firm had previously conducted an acceptable bioequivalence study under fasting conditions on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg Capsule (submission dated June 16, 1995). The firm was asked to submit a post-prandial bioequivalence study as condition of approval (Agency's letter dated January 31, 1996).

II. Background:

Triamterene/hydrochlorothiazide is a diuretic/antihypertensive drug that combines natriuretic and antikaliuretic effects. It is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone. Each component complements the action of the other. The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. The triamterene component inhibits the reabsorption of sodium in exchange for potassium and hydrogen ions.

Triamterene is rapidly absorbed from GI tract; however, the degree of absorption varies in different individuals. Peak plasma concentrations of 0.05-0.28 ug/mL are achieved within 2-4 hours following administration of 100 to 200 mg single oral dose. The plasma half-life of triamterene is 100-150 minutes. The metabolic and excretory fate of triamterene has not been fully determined. The drug is reportedly metabolized to 6-p-hydroxytriamterene and its sulfate conjugate. Triamterene is excreted in urine as unchanged drug and metabolites. In one study in healthy males, the urinary excretion of 6-p-hydroxytriamterene was up 3 times that of unchanged drug. The formed hydroxytriamterene sulfate is pharmacologically active.
Hydrochlorothiazide (HCTZ) is widely used in the treatment of

hypertension. It is rapidly absorbed from the gastrointestinal tract with peak concentrations occurring approximately 1 to 3 hours after dosing. Elimination of HCTZ from the body occurs via excretion of unchanged drug in the urine, with reported elimination half-life of 3 to 9 hours. The onset of diuresis following an acute dose of HCTZ corresponds well with plasma drug concentration, occurring within 12 hours after administration and is essentially complete within 12 hours of a dose.
In a limited study involving 12 subjects, coadministration of Dyazide^{R} (Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsule) with a high-fat meal resulted in: 1) an increase in the mean bioavailability of triamterene by about 67%, p-hydroxytriamterene sulfate by about 50%, hydrochlorothiazide by about 17%; 2) increase in the peak concentrations of triamterene and p-hydroxytriamterene; and 3) a delay of up to 2 hours in the absorption of the active constituents.
Triamterene/Hydrochlorothiazide combination products are available as oral capsules (37.5 mg/25 mg strength) and oral tablets (75mg/50mg and 37.5mg/25 mg strengths).

III. Single Dose Post-Prandial Bioequivalence Study #DYAZ-9519:

Clinical site:	(b)4 - Confidential Business
Analytical site:	(b)4 - Confidential Business
Investigators:	(b)4 - Confidential Principal Investigator
Study design:	Open-label, randomized, 3-way crossover, single-dose study under fasting and nonfasting conditions.
Study date:	Clinical phase: April 1, 1995 through April 18, 1995. Analytical phase: April 19, 1995 through May 22, 1995.
Subjects:	Twenty (20) male subjects between 18 to 45 years of age were accepted for entry into the clinical portion of the study. Eighteen (18) subjects reported for dosing in period I. All eighteen successfully completed the three periods of the study. All subjects were within ±10% of desirable weight for their height and body frame as described in the Metropolitan Life Insurance Bulletin, 1983. The subjects were selected on the basis of acceptable medical histories and normal physical examinations that showed no clinically significant chronic disease.

Exclusion criteria:	* History of adverse reactions or allergy to triamterene, hydrochlorothiazide, sulfa drugs, and other thiazide diuretics. * Presence of any clinically relevant abnormality identified on the screening physical or laboratory examinations. * Any subject who has received an investigational drug within four weeks prior to entry into the study.
Restrictions:	Subjects were instructed not to take any medications, including aspirin and OTC preparations from two weeks prior to the first drug administration until after the study. Alcohol, xanthine-or caffeine containing beverages and food prohibited from 48 hours prior to dosing and until after completion of the study.
Dose and treatment:	All subjects completed an overnight fast.
Treatment A: (nonfasting)	2 x 37.5 mg/25 mg Triamterene/Hydrochlorothiazide, capsules (Mylan), lot #23A004N
Treatment B: (nonfasting)	2 x 37.5 mg/25 mg Dyazide^{R} capsules (Smith Kline Beecham), lot #124E50, Exp. 3/96.
Treatment C: (fasting)	2 x 37.5 mg/25 mg Triamterene/Hydrochlorothiazide capsules (Mylan), lot #23A004N.
Food and fluid intake:	Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen C ingested the capsules with 240 mL of water. Subjects on regimen A and B ingested the capsules with 240 mL of water within 30 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Liquids were ad libitum except within 2 hours of drug administration.
Blood samples:	Blood samples were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48

and 72 hours. Plasma was separated and promptly frozen for analysis of triamterene, triamterene sulfate and hydrochlorothiazide.

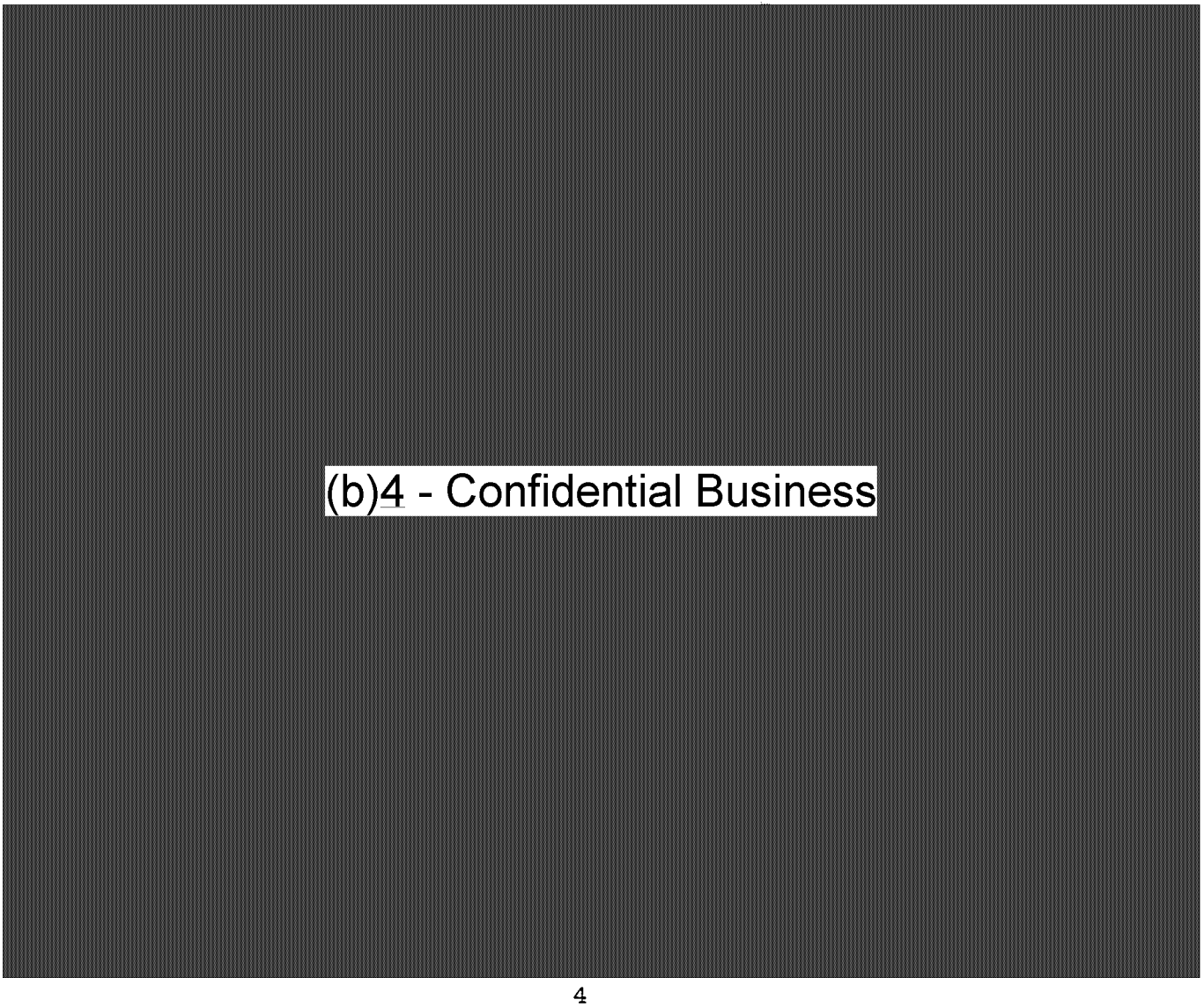
Urine samples: Urine samples were collected (-1-0, 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48 and 48-72 hours) but were not analyzed.

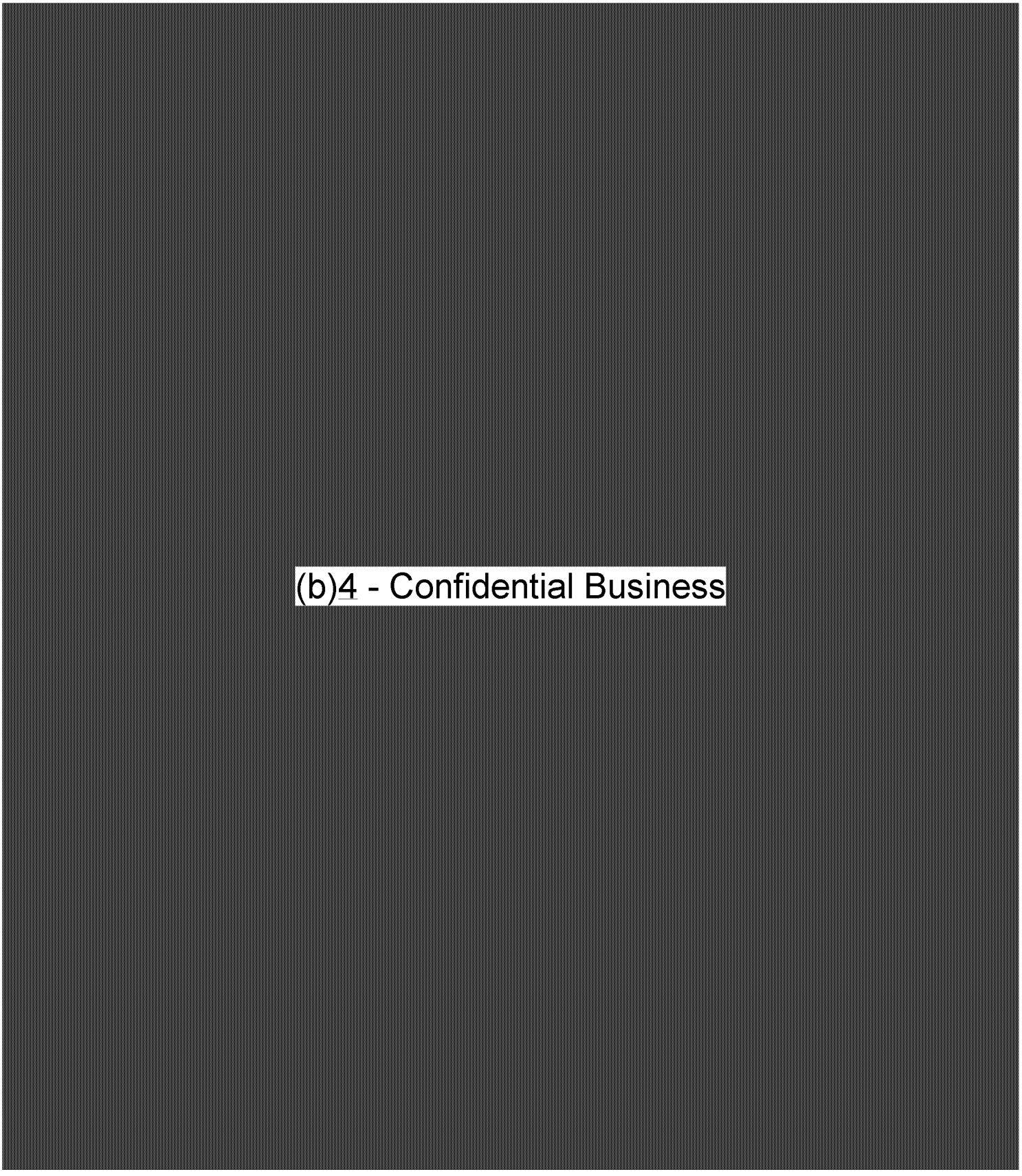
Subjects welfare: Vital signs (including blood pressure, pulse and respiration rates) were measured hourly for eight hours after dosing and at 10, 12, 24, 48 and 72 hours.

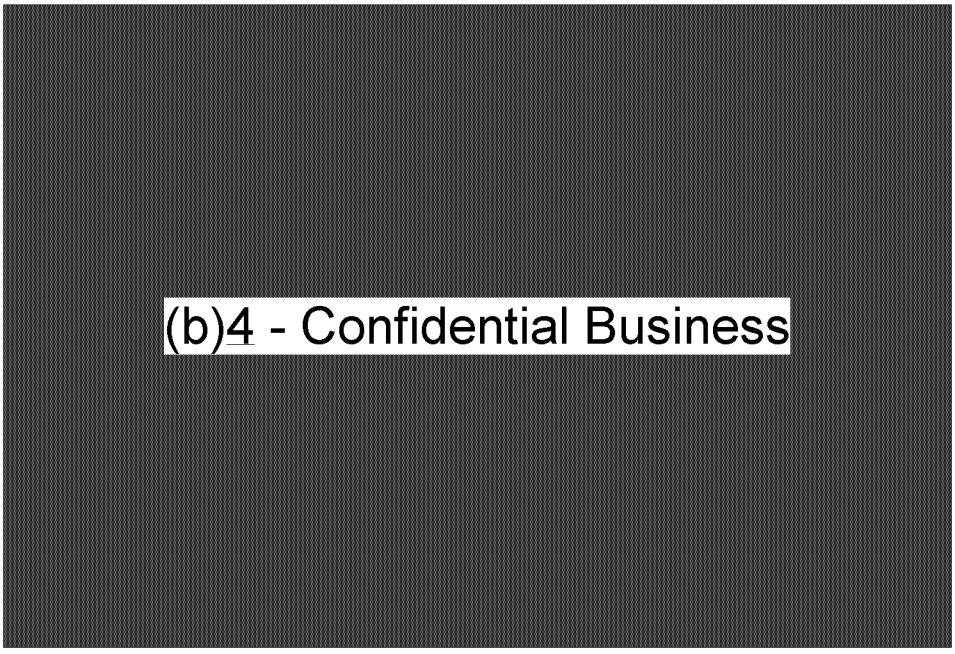
Washout period: One week.

Analytical Methodology

a. Plasma Triamterene and Triamterene Sulfate




(b)4 - Confidential Business



Statistical Analysis

Statistical analysis was performed on triamterene, triamterene sulfate and hydrochlorothiazide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The data analyzed by ANOVA were also performed for blood drug concentrations at each sampling time.

IV. In Vivo Results:

Twenty (20) healthy male subjects were accepted for entry into the clinical phase of the study. Eighteen (18) subjects reported for dosing in period I. All eighteen successfully completed three phases of the study. Two subjects did not report for phase I dosing. Four adverse events were reported; two were considered possibly drug related and two remotely drug related by the clinician. Subject #8 complained of headache. Subject #14 complained of lightheadedness and nausea.

Three blood samples could not be drawn because the subject was absent. This occurred for subject #10 (period I, treatment A, 36.0 hour), subject #16 (period I, treatment A, 72 hour), and subject #3 (period II, treatment C, 72 hour).

The plasma levels and pharmacokinetic parameters for triamterene, triamterene sulfate and hydrochlorothiazide are summarized below:

Table I

Mean Plasma Triamterene Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 75 mg/50 mg Triamterene/Hydrochlorothiazide (2X37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions
(N=18)

Time hr	A Mylan Test Product Lot# 23A004N Nonfasting ng/mL (SD)	B SmithKline Reference Product Lot #124E50 Nonfasting ng/mL (SD)	C Mylan Test Product Lot #23A004N Fasting ng/mL (SD)
0	0.00	0.00	0.00
0.25	0.59(1.3)	8.02 (17.3)	27.79(43.3)
0.5	9.87(9.2)	32.87 (44.7)	139.01(82.7)
0.75	26.79(20.4)	49.97 (54.3)	161.70(73.5)
1	41.96(29.4)	71.59 (61.9)	156.04(75.9)
1.25	57.94(31.6)	91.27 (64.5)	124.03(51.7)
1.5	75.86(37.6)	102.46 (53.8)	110.70(44.6)
2	100.92(42.8)	120.25 (56.1)	87.93(38.0)
2.5	111.87(50.6)	117.33 (47.6)	76.60(32.5)
3	111.90(47.6)	113.08 (42.0)	65.87(30.5)
3.5	106.15(40.0)	103.47 (41.6)	57.50(28.7)
4	105.46(44.2)	88.39 (37.5)	50.34(25.2)
4.5	83.08(35.9)	77.04 (38.2)	41.78(19.9)
5	73.87(31.8)	62.32 (26.7)	37.39(18.8)
6	44.84(19.2)	39.06 (22.1)	22.82(11.8)
8	20.06(9.9)	18.56 (12.5)	12.18(6.6)
10	11.53(6.8)	10.32 (6.5)	7.54(3.8)
12	6.35(3.8)	5.49 (3.4)	5.07(2.9)
16	2.25(1.9)	2.45 (1.9)	2.69(1.7)
24	0.42(0.7)	0.51 (0.7)	1.28(1.4)
36	0.08(0.3)	0.00 (0.0)	0.44(0.8)
48	0.18(0.8)	0.00 (0.0)	0.13(0.4)
72	0.00(0.0)	0.00 (0.0)	0.19(0.8)
	Mean (CV)	Mean (CV)	Mean (CV) A/B
AUC(0-t) ng.hr/mL	589.55(38.5)	603.93(44.4)	531.62(42.2) 0.98
AUCinf ng.hr/mL	598.96(38.3)	612.34(43.9)	545.68(41.9) 0.98
Cpeak (ng/mL)	132.61(32.9)	140.51(40.2)	176.67(44.5) 0.94
Kel (1/hr)	0.237	0.223	0.165
Half (hr)	3.18	3.56	5.40
Tpeak(hr)	2.83	2.28	0.76

Plasma Triamterene:

1. The triamterene plasma levels peaked at 3 and 2 hours for the test and the reference products, respectively, under nonfasting conditions.

2. For Mylan test product, the means AUC(0-t), AUCinf and Cpeak values are 2.4%, 2.2% and 5.6% lower, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak.

3. The mean AUC(0-t) of the test product was increased by 11% and the mean Cpeak was reduced by 25%, when dosed under nonfasting conditions compared to fasting conditions. This increase in AUC value is in agreement with the reference product's data (PDR) which indicated that food intake increases the mean bioavailability of triamterene and causes a delay of up to 2 hours in the absorption of the active constituents. However, the study data shows that food intake resulted in a decrease in the Cpeak value instead of an increase.

4. Clinical vital signs were analyzed for statistical differences; these include systolic and diastolic blood pressure, heart rate and respiration. There were no clinically significant differences in the parameters evaluated.

Table II

Mean Plasma Triamterene Sulfate Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 75 mg/50 mg Triamterene/Hydrochlorothiazide (2x37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions (N=18)

Time hr	A Mylan Test Product Lot# 23A004N Nonfasting ng/mL (SD)	B SmithKline Reference Product Lot #124E50 Nonfasting ng/mL (SD)	C Mylan Test Product Lot #23A004N Fasting ng/mL (SD)
0	0.00	0.00	0.00
0.25	0.00	5.22 (13)	28.79(47)
0.5	23.21(20)	111.33 (159)	504.49(329)
0.75	127.61(114)	258.00 (263)	957.82(424)
1	258.76(246)	393.98 (292)	1092.35(461)
1.25	372.31(273)	532.06 (256)	1034.69(453)
1.5	524.46(334)	661.90 (219)	951.97(412)
2	776.99(330)	864.54 (229)	738.48(272)
2.5	874.43(293)	946.67 (259)	606.52(214)

3	929.14(280)	907.29 (219)	488.89(176)
3.5	874.60(245)	845.88 (269)	394.25(132)
4	888.00(360)	735.75 (309)	333.97(120)
4.5	666.39(222)	605.86 (276)	257.79(80)
5	578.99(201)	472.21 (199)	224.79(73)
6	385.10(139)	317.36 (128)	169.93(47)
8	159.54(52)	139.11 (53)	90.70(29)
10	84.72(35)	71.82 (25)	54.57(21)
12	50.16(19)	41.69 (17)	40.27(19)
16	14.43(11)	13.22 (11)	18.69(14)
24	1.12(5)	0.00	4.36(11)
36	0.00	0.00	0.93(4)
48	0.00	0.00	0.00
72	0.00	0.00	1.76(7)

	Mean (CV)	Mean (CV)	Mean (CV)	A/B
AUC(0-t) ng.hr/mL	4564(24)	4408(23)	3618(29)	1.03
AUCinf ng.hr/mL	4662(24)	4505(23)	3774(28)	1.03
Cpeak (ng/mL)	1080(31)	1071(24)	1119(42)	1.01
Kel (1/hr)	0.262	0.261	0.181	
Half (hr)	2.88	2.76	4.60	
Tpeak(hr)	3.08	2.57	1.03	

Plasma Triamterene Sulfate

1. The triamterene sulfate plasma levels peaked at 2.5 and 3 hours for the reference and test products, respectively, under nonfasting conditions.

2. For Mylan test product, the means AUC(0-t), AUCinf and Cpeak values are 3.5%, 3.5% and 0.8% higher, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak.

3. The mean AUC(0-t) of the test product was increased by 26% and the mean Cpeak was reduced by 3.5%, when dosed under nonfasting conditions compared to fasting conditions. This increase in AUC value is in agreement with the reference product's data (PDR) which indicated that food intake increases the mean bioavailability of triamterene sulfate and causes a delay of up to 2 hours in the absorption of the active constituents. However, the study data shows that food intake resulted in a decrease in the Cpeak value instead of an increase.

Table III

Mean Plasma Hydrochlorothiazide Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 75 mg/50 mg Triamterene/Hydrochlorothiazide (2x37.5mg/25 mg Capsules) Under Fasting and Nonfasting Conditions (N=18)

Time hr	A Mylan Test Product Lot# 23A004N Nonfasting ng/mL (SD)	B SmithKline Reference Product Lot #124E50 Nonfasting ng/mL (SD)	C Mylan Test Product Lot #23A004N Fasting ng/mL (SD)
0	0.00	0.00	0.00
0.25	0.00	0.75 (2.2)	2.12(6)
0.5	1.49(2.9)	13.99 (22.9)	52.26(36)
0.75	11.71(11.7)	37.16 (45.2)	149.80(57)
1	30.86(25.6)	68.76 (62.1)	240.14(83)
1.25	52.51(34.6)	104.28 (64.7)	273.53(102)
1.5	84.23(48.9)	136.04 (61.6)	269.63(92)
2	132.92(51.4)	186.63 (51.3)	246.39(72)
2.5	173.99(43.8)	211.39 (46.7)	221.52(57)
3	205.77(51.1)	220.28 (42.1)	198.51(51)
3.5	217.53(45.4)	219.84 (37.6)	171.65(39)
4	212.54(48.3)	206.18 (43.0)	157.76(36)
4.5	197.88(51.3)	185.04 (39.5)	141.21(32)
5	185.33(50.5)	165.88 (36.7)	126.98(32)
6	137.60(34.3)	124.92 (33.5)	89.87(21)
8	77.39(16.4)	72.41 (18.1)	59.37(14)
10	55.21(12.0)	54.15 (13.0)	46.23(10)
12	42.72(9.5)	42.08 (10.3)	36.23(10)
16	30.50(7.2)	30.67 (8.7)	26.42(7)
24	18.97(4.9)	20.00 (7.5)	16.77(5)
36	8.25(3.2)	9.01 (5.8)	6.78(4)
48	1.27(2.9)	3.39 (4.9)	0.29(1)
72	0.00	0.00	0.00
	Mean (CV)	Mean (CV)	Mean (CV) A/B
AUC(0-t) ng.hr/mL	1797(20)	1893(21)	1761(23) 0.95
AUCinf ng.hr/mL	1927(20)	2101(26)	1895(21) 0.92
Cpeak (ng/mL)	231(22)	241(17)	291(32) 0.96
Kel (1/hr)	0.065	0.058	0.064
Half (hr)	10.9	14.3	11.1
Tpeak(hr)	3.44	3.03	1.75

Plasma Hydrochlorothiazide

1. The hydrochlorothiazide plasma levels peaked at 3 and 3.5 hours for the reference and test products, respectively, under nonfasting conditions.

2. For Mylan test product, the means AUC(0-t), AUCinf and Cpeak values are 5.1%, 8.3% and 4.1% lower, respectively, than those for the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak.

V. In Vitro Dissolution Testing

Method:	USP 23 apparatus 2 at 100 rpm
Medium:	900 mL of 0.1 M acetic acid containing 1% of polysorbate 20.
Sampling Time:	0.5, 1, 1.5 and 2 hours
Number of Capsules:	12
Test Product:	Mylan's triamterene/hydrochlorothiazide 37.5mg/25 mg capsules, lot # 23A004N
Reference product:	SmithKline Beecham's Dyazide^{R} 37.5 mg/25 mg capsules, lot # 124E50.

The dissolution testing results are presented in Table IV.

VI. Comments:

1. The firm's in vivo single-dose bioequivalence study #DYAZ-9519 on its triamterene/hydrochlorothiazide 37.5 mg/25 mg capsule under fasting and nonfasting conditions is acceptable. The ratios of the test mean to the reference mean for triamterene, triamterene sulfate and hydrochlorothiazide were within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak under nonfasting conditions.

2. The in vitro dissolution testing submitted by the firm on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg Capsules is acceptable.

3. The firm had previously conducted an acceptable bioequivalence study under fasting conditions on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg Capsule (submission dated June 16, 1995).

VII. Recommendations:

1. The single-dose bioequivalence study #DYAZ-9519 under fasting

and nonfasting conditions conducted by Mylan Pharmaceuticals Inc., on its Triamterene/Hydrochlorothiazide 37.5 mg/25 mg capsule, lot #23A004N, comparing it to Dyazide^{R} 37.5 mg/25 mg capsule, manufactured by SmithKine Beecham., has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Triamterene/Hydrochlorothiazide Capsule, 37.5 mg/25 mg is bioequivalent to the reference product, Dyazide^{R}, 37.5 mg/25 mg Capsule, manufactured by SmithKline Beecham.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its triamterene/hydrochlorothiazide 37.5 mg/25 mg capsule, lot #23A004N, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 M acetic acid containing 1% of polysorbate 20, at 37^{0}C using USP 23 apparatus 2 (paddle) at 100 rpm. The test product should meet the following specifications:

NLT (b)4 in 120 minutes for Hydrochlorothiazide
NLT (b)4 in 120 minutes for Triamterene

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is acceptable.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/ Date: 5/22/96
FT INITIALLED RMHATRE

(b)4 - Confidential Business

Concur: _____ Date: 5/24/96
[redacted], Ph.D.
Director
Division of Bioequivalence

MMakary/5-22-96 wp 74701SD.296
cc: ANDA #74-701,original, HFD-600(Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table IV In Vitro Dissolution Testing

Drug (Generic Name): Triamterene/Hydrochlorothiazide
Dose Strength: 37.5 mg/25 mg Capsules
ANDA No.:74-701
Firm: Mylan Pharmaceuticals Inc.
Submission Date: February 7, 1996
File Name: 74701SD.695

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 100
No. Units Tested: 12 Capsules
Medium:900 mL of 0.1 M Acetic Acid containing 1% of polysorbate 2(b)
Specifications: NLT [redacted] of the labeled amounts of triamterene and hydrochlorothiazide are dissolved in 120 minutes.
Reference Drug: Dyazide
Assay Methodology [redacted](b)4 - Confidential[redacted]

II. Results of In Vitro Dissolution Testing: Triamterene

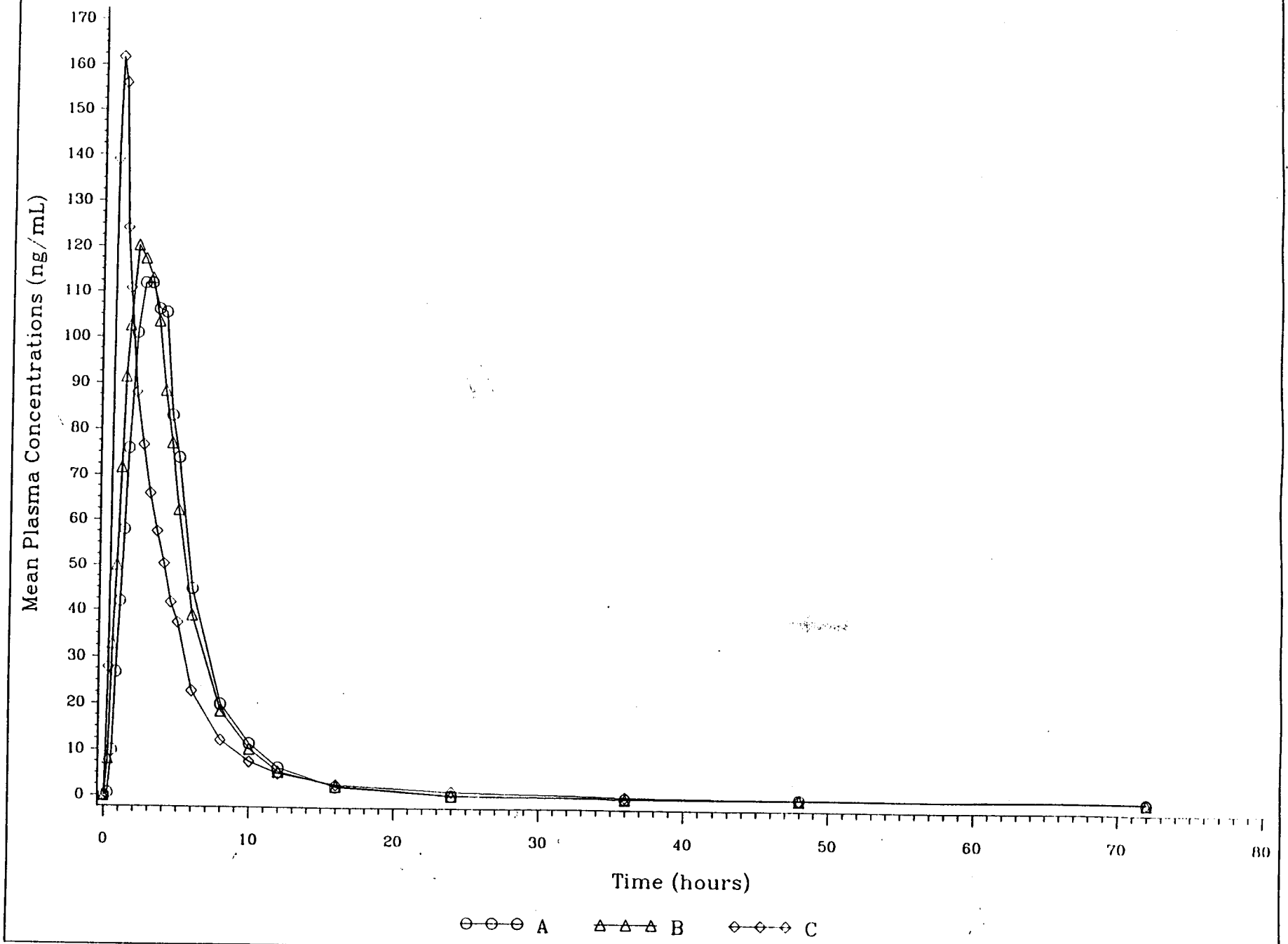
Sampling Times (hour)	Test Product Lot # 23A004N Strength(mg) 37.5/25			Reference Product Lot #124E50 Strength(mg) 37.5/25		
	Mean %	Range	%CV	Mean %	Range	%CV
0.5	97.2	[redacted](b)4 - Confidential Business	1.5	100.3	[redacted](b)4 - Confidential Business	4.6
1	97.7		1.6	102.0		2.3
1.5	98.0		1.7	102.6		2.6
2	98.3		1.6	102.5		2.3

Hydrochlorothiazide

Sampling Times (hour)	Test Product Lot # 23A004N Strength(mg) 37.5/25			Reference Product Lot #124E50 Strength(mg) 37.5/25		
	Mean %	Range	%CV	Mean %	Range	%CV
0.5	95.3	[redacted](b)4 - Confidential Business	3.2	98.7	[redacted](b)4 - Confidential Business	4.4
1	95.9		3.2	101.0		2.2
1.5	96.5		3.6	101.6		3.0
2	95.8		2.4	101.2		2.2

DYAZIDE (DYAZ-9519)

Mean Triamterene Plasma Concentrations

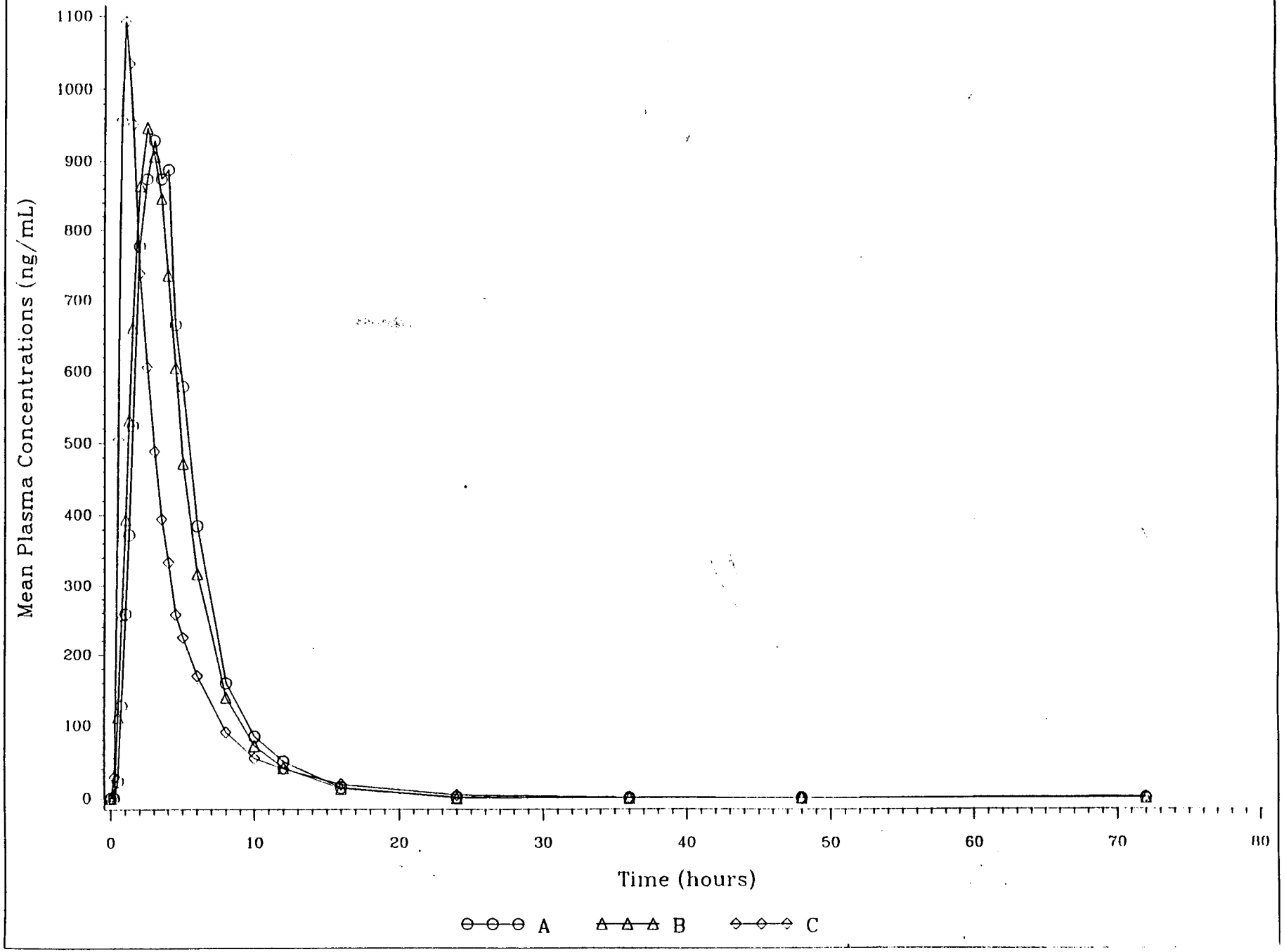


HC

ATTACHMENT 1

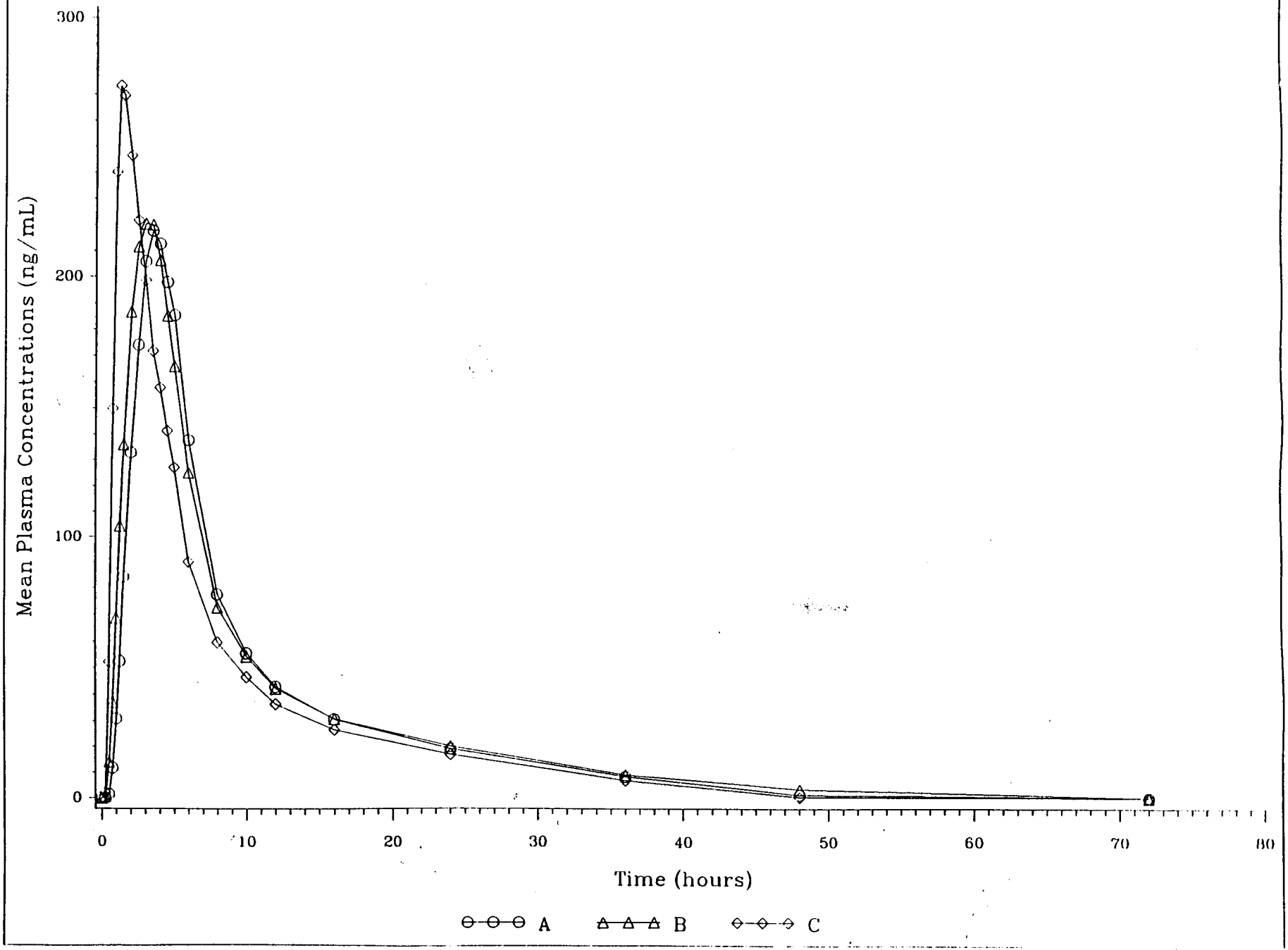
DIAZIDE (DIAZ [illegible])

Mean TS04 Plasma Concentrations



DYAZIDE (DYAZ-9519)

Mean HCTZ Plasma Concentrations



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ATTACHMENT 1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-701 SPONSOR: Mylan Pharmaceutical
DRUG: Triamterene / Hydrochlorothiazide
DOSAGE FORM: ~~37.5mg~~ Capsules
STRENGTH(s): 37.5 mg/25 mg
TYPE OF STUDY: Single/~~Multiple~~ ~~Fasting~~/Fed
STUDY SITE: [redacted] (b)4 - Confidential Business

STUDY SUMMARY: The bioequivalence studies under fasting and nonfasting conditions are acceptable. The 90% CI for AUC(0-t), AUCi and Cmax are within the acceptable range of 80-120 % for the fasting study. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for the above parameters under non fasting condition.

DISSOLUTION: Dissolution Testing is acceptable

PRIMARY REVIEWER: [redacted] BRANCH: III

INITIAL: [redacted] /S/ DATE: 5/22/96

BRANCH CHIEF: BRANCH:

INITIAL: [redacted] /S/ DATE: 5/22/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: [redacted] /S/ DATE: 6/3/96

DIRECTOR
~~OFFICE OF GENERIC DRUGS~~ OPS (first approval)

INITIAL: DATE: